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Editorial

Counting on big numbers

In recent months the UK Biobank project – now up and running in cities across the country – reached a landmark in its recruitment of 500,000 people. Research on their wellbeing and lifestyle habits will help to improve the health of future generations.

The 250,000th person – the halfway marker – went through the 90-min assessment several months ago, putting the project on target to complete the recruitment of its half million participants in mid 2010, on budget and on schedule.

Rory Collins, UK Biobank's Principal Investigator and British Heart Foundation Professor of Medicine, Oxford University, said he has been delighted to see such a positive, and generous, response to this project. Around one in ten people invited to join the UK Biobank takes part in the project; one in 120 individuals across the country will be participants by the time recruitment comes to an end. "It is satisfying to know that so many people will go out of their way to help people they will never know," commented Professor Collins.

His remarks were endorsed by Sir Mark Walport, Director of the Wellcome Trust, one of the main funders of the project. He said that the success of the UK Biobank in recruiting 250,000 individuals showed how willing and keen people are to participate in medical research.

> "The greatest improvements in human health have come from implementing better public health measures combined with modern medicines," he said. "UK Biobank is a crucial project for advancing public health in the 21st century."

UK Biobank is a long-term prospective epidemiological study; one of the largest of its kind, and certainly the most detailed. It has grown out of a great research tradition that has shaped knowledge and understanding of a number of common diseases that disable and kill, including cancer and heart disease.

The project's goal is to build a resource to 'improve the health of future generations'. The resource will be open to all researchers who meet the relevant ethical and scientific criteria in place to allow access. Researchers will be required to put findings based on the resource back into the public domain for all to benefit.

UK Biobank is funded by the UK Medical Research Council, Wellcome Trust, Department of Health, Scottish Government, Welsh Assembly Government and the Northwest Regional Development Agency. With their backing, UK Biobank was provided with independent charity status to give the resource a stable structure over the coming decades. It has the support of the NHS, Royal College of General Practitioners, and a number of the country's leading medical charities, including the British Heart Foundation, Cancer Research UK, British Lung Foundation, Diabetes UK and the Arthritis Research Campaign. UK Biobank is a collaborative effort of more than 20 UK universities, and constantly looks to involve an ever-growing number of experts from the UK (and overseas) health research community.

1. The power of prospective epidemiology

Almost 60 years ago the eminent scientist the late Sir Richard Doll embarked on a project to find out what caused lung cancer and in a pioneering study he followed the lives and deaths of 40,000 doctors. His work proved the link between smoking and lung cancer; evidence that has gone on to save many millions of lives worldwide.

Sir Richard's powerful study[1,2] has gone on to reveal the strength with which smoking is linked to a number of cancers, and helped identify the role that smoking plays in heart disease, stroke and many other life-threatening disorders. Many of Sir Richard's findings were unexpected at the time of his study.

Other studies that have followed individuals' health have gone on to be equally important in the understanding of disease development, and in helping to improve treatment. The Framingham Heart Study of just 5000 people recruited in 1948 from this eponymous Massachusetts town has gone on to provide lots of important information on cardiovascular disease.

UK Biobank has taken these studies as a lead – but seeks to expand them many times over with the aim of providing an exciting and detailed resource for health researchers for many decades to come.

Not only is the UK Biobank collecting valuable baseline data from participants, but it will track their health over the next 30 years. The resource will also include samples of blood and urine and body measurements for researchers to study. Overall, the repository will include around 500 data points for every individual (250 million overall), that will be stored and, ultimately, be available for research.

The ability to analyse biological samples, including for genes and a variety of other markers, taken before diseases occurred will provide a powerful and exciting research tool for a wide range of common, life-threatening illnesses.

2. Nature and nurture: the complex mix

Participants in the UK Biobank are aged between 40 and 69 years. This age includes people young enough for scientists to be able to study exposures prior to the development of disease while still at risk over the next few decades of developing a wide range of important diseases (including cancer, heart disease, stroke, diabetes and dementia).

With the explosion in understanding of the way in which bodies function at a cellular level, and the complex interaction between

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genes and lifestyles, a resource such as the UK Biobank will provide a deep vein of health-related information for health scientists for many years to come.

By about the end of the first decade (i.e. around 2016) the UK Biobank will have recorded about 20,000 cases of diabetes mellitus, more than 10,000 cases of MI and coronary death, more than 5000 cases of COPD, and 5000 cases of breast cancer. By the fifteenth year of follow-up there will also be at least 5000 cases of stroke, Alzheimer's disease, Parkinson's disease, colorectal cancer and prostate cancer. In other words, the UK Biobank will have generated at least 5000 incident cases for eight common disorders by about 2020, and so should be sufficiently mature to allow reliable assessment of the determinants of these conditions. Moreover, it will also have generated similar numbers of cases of a range of other important conditions, and these numbers will continue to increase as follow-up though health-care records continues.

> "With the recruitment of 500,000 middle-aged adults, UK Biobank will provide a powerful platform for studying a range of complex diseases that are of great relevance to public health," said Dr Tim Sprosen, UK Biobank Chief Scientist.
> "By maintaining close and active contact with other similar resources, UK Biobank can also ensure that it is in a position to make a major contribution to collaborative initiatives to support the investigation of rarer conditions."

3. Roll out

Such a visionary project – to build a major resource for health scientists – got properly underway in April 2007, with the opening of the UK Biobank's first assessment centre in Manchester. A pilot study took place in Altrincham the year before.

Over the course of the past 2 years the project has rolled out across the country, recruiting in Oxford, Cardiff, Glasgow, Edinburgh, Stoke, Reading, Bury, Newcastle, Leeds, Liverpool, Bristol, Nottingham and London City.

Participation starts with the receipt of a letter of invitation. Letters are mailed over a 9-month–1-year time frame to all people in the relevant age group within about a 15–20 mile radius of the centrally located assessment centre. Contact details for the purposes of inviting people to take part are provided centrally by the NHS (with the relevant approvals from ethics committees and the Patient Information Advisory Group, PIAG). People are provided with a provisional appointment time and date, which can be changed very easily to a more convenient time, if necessary, by calling the UK Biobank's free phone Participant Resource Centre, based at Cardiff University.

On arrival at an assessment centre, participants are asked to give their consent to joining the project (including long-term health follow-up), before starting on a 45-min touch screen questionnaire about their current health and lifestyle. This includes a very wide range of questions, from the colour of one's hair or skin, the speed at which they drive, the number of sexual partners they have had and the sort of house in which they live.

Participants are then interviewed by a trained nurse about more specific aspects of their health, such as the number and type of operations they may have had and the medication they take. The nurse also takes their blood pressure. The next step is the measurements booth, where participants are weighed and measured, have their hand-grip and lungs tested and have the bone density in their heel recorded by ultrasound. Participants then provide a small donation of blood (50 ml) and a urine sample, before stopping for a cup of tea and a biscuit and heading out of the door.

The completed visit takes about 90 min, and participants are provided with a list of their measurements and some attempt to put them into context. UK Biobank is not a health check, and provides no further feedback on health either at this stage or later on in the project (indeed, no analysis will be undertaken on blood and urine samples for many years. To provide feedback at a later date is ethically and practically very difficult to do).

Personal information is sent via secure networks to the UK Biobank computer systems, where it is stripped of identification and stored securely for many years. In due course, a small team will match updated health information with individual records, but only properly anonymised information will be provided to scientists using the resource.

4. Safe and sound

System security and the retention of participant anonymity over many years are key concerns for the UK Biobank. Dr Sprosen said:

> "We understand that people participate because they want to rather than because they have to. Participation is about trust, believing in the project and believing that people's most private information is safe with us. The entire credibility of the project rests with the way in which we approach security of data because participants can withdraw at any time."
> "To that end, I believe UK Biobank has in place the processes and mechanisms to ensure that our systems are safe and participants are protected."

As a small, tight-knit research project UK Biobank can closely control and monitor its security systems, which meet and go beyond industry standards. IT security was part of the agreement between the project and the NHS, and PIAG. These agreements include a review of system security. UK Biobank also works with the National Computing Company for its IT security review. This includes penetration testing and support as the UK Biobank moves towards ISO/IEC 27001 accreditation. Access to systems is carefully controlled by usernames and passwords, systems are designed to prevent abuse and the project continuously reviews these systems for potential flaws. Staff with access to the invitations and appointments systems have no access to data collected at the assessment centre sites (which are encrypted).

5. Archive facility

No archive resource would be of any use without the proper storage of biological materials and the ability to retrieve quickly and accurately those blood and urine samples that may be stored for many years.

Blood and urine samples, collected in 1 day from up to seven operating assessment centres at any one time, are shipped overnight to purpose-built storage facilities near Manchester. By mid-afternoon the following day blood samples are further sub-divided into aliquots (using the latest robotics technology) and both blood and urine samples are stored at temperatures down to $-200\,^{\circ}C$. Bar-coded test-tubes stored in ultra-dry conditions mean that each sample will be clearly identifiable to the computer-controlled robotic retrieval system which will fish out the required samples overnight as scientists draw on the facility.

The state-of-the-art archive system was a finalist in the 2008 MacRobert Award for Engineering, run by the Royal Academy of Engineering and was recently officially opened by HRH The Princess Royal. The system is fed constantly by the two largest nitrogen tanks in the country, keeping the samples safe for decades to come.

6. Communications

By the time the UK Biobank finishes its recruitment it will have written to around one quarter of all 40–69 year-olds living in Britain. Every 1 in 120 people will be participants (around 1% of the adult British population) – and all these individuals will have passed through the assessment centre process. The sheer size and scale of the project has required a sensitive and responsive communications strategy and one that will lend itself to on-going communication with a large body of participants, scientists, media and the general public over many decades.

In their letters of invitation, people are provided with a provisional appointment time and date at their local UK Biobank assessment centre. People are asked to confirm (or cancel) using the website, a pre-paid reply slip or by calling the UK Biobank free phone Participant Resource Centre (PRC), open 6 days a week, 8 am–7 pm.

The PRC, operated by Cardiff University, has taken almost 400,000 phone calls and dealt with many letters and emails from people wanting to know more about the project. The most common question is about finding one's way to the assessment centre, but it also takes calls on confidentiality, data security, expenses (which are payable), and so on.

UK Biobank also writes to all GPs and practice managers in areas within which it is about to recruit, informing them of the project. GPs and practice managers are invited to an informal meeting at the assessment centre one evening before it opens.

The project also embarks on a media campaign, priming people to look out for their letters of invitation. This campaign includes side-of-bus advertising and inviting press along to the first day of recruitment. Letters to councils, medical committees and local health and volunteer groups are also sent out.

> "It is important that people are aware of UK Biobank, so that when the invitation slips through their letterbox it does not come as a complete surprise," explained Dr Sprosen. "We know that coming to UK Biobank is a big ask. People have to actively respond positively, put the date in their diary, possibly book time off work and then remember to come on the day. That they take the time and trouble to do this, and do this without expecting anything in return, is enormously encouraging to us, and should be very encouraging to researchers more generally." "The key point is that when people feel properly informed – and UK Biobank goes out of its way to do this – they will respond in the positive. Perhaps that is one of the most important findings to come out of UK Biobank, and so soon: people support research – and they will do so in great numbers if they have the right information to hand."

UK Biobank has recently received additional funding of £6 million from the Wellcome Trust, Medical Research Council and Department of Health, to allow for improved phenotyping. This includes the collection of more information about participants' diets, the collection of saliva sample, an additional sample of blood to study RNA, and the provision of facilities to record information on participants' eyes. UK Biobank will also go back to some participants to gather further baseline information and a web-based diet questionnaire is planned.

"UK Biobank is one of the biggest, but certainly the most detailed study of its kind," said Dr Sprosen. "I am grateful to everyone who has participated and welcome those yet to join the project."

7. Ethics and governance

The interests of participants and the public are at the heart of the UK Biobank. An Ethics & Governance Framework (EGF) was established to make sure that participants are protected, and that the resource is used only for scientifically and ethically approved research. UK Biobank's independent Ethics and Governance Council, chaired by Professor Graeme Laurie, University of Edinburgh, oversees the UK Biobank's adherence to the EGF. The Council takes a close interest in security of the project and will also be involved with developing the detailed access procedures allowing scientists to use the resource. The EGC can be contacted via its website at http://www.egcukbiobank.org.uk or by writing to UK Biobank EGC, Wellcome Trust, 215 Euston Road, London, NW1 2BE telephone 020 7611 8888.

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Conflicts of interest
None declared.

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